1 PROTOCOL SYNOPSIS

1.1 Title:

A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T cells with and without Exogenous Interleukin-2 in HIV-Infected Patients.

1.2 Sponsors:

University of Pennsylvania
Cell Genesys, Inc.

1.3 Drug/IND's:

CD4-zeta gene-modified, costimulated and ex vivo expanded autologous CD4+ T lymphocytes (INDs # 6585 and #6675).

1.4 Indication:

Infection with HIV-1 with undetectable viral load on HAART therapy for > 8 weeks

1.5 Primary Objectives:

1. Assess the safety, tolerability and feasibility of administering an infusion of autologous CD4-zeta gene-modified CD4+T cells in an outpatient setting of highly active antiretroviral therapy (HAART) with and without IL-2 at a maximum non-toxic daily dose of ~ 1.2M IU/m^2 subcutaneously daily for 56 days.

2. Assess the effect of daily subcutaneous IL-2 on the persistence and trafficking of CD4-zeta gene-modified T cells in the circulation and lymphoid (rectal) tissue.

3. Determine the effect of CD4-zeta infusions with and without IL-2 on viral load (plasma HIV-1 RNA, tissue HIV-1 RNA, and frequency of latent replication-competent HIV-1 in PBMC).

1.6 Secondary Objectives

1. Determine the "helper" effect of CD4-zeta infusions on lymphocyte function
   - LPA to mitogens, CMV and HIV env and gag
   - CTL
   - Neutralizing antibody in plasma
2. Determine effect of IL-2 on CD4 naïve and memory lymphocytes .
   - Assess the surface phenotype of the infused CD4-zeta marked cells
   - Determine if IL-2 affects the reversion rate of CD4-zeta marked cells to cells with naïve phenotypes

1.7 Study Design:

A three-arm, randomized study of gene-modified costimulated T cells with or without daily subcutaneous IL-2 in patients with stable or undetectable viral load. The interventional duration of the study will be 16 weeks.

1.8 Dose, Schedule & Route:

Arm 1. Patients continue HAART and receive low dose rIL-2 (~ 1.2M IU/m^2) sq daily x 56 days

Arm 2: Patients continue HAART and receive approximately 10^{10} CD4-zeta gene modified CD4+ T cells by IV infusion.

Arm 3: Patients continue HAART and receive approximately 10^{10} CD4-zeta gene modified CD4+ T cells by IV infusion and low dose rIL-2 (~ 1.2M IU/m^2) sq daily x 56 days.

1.9 Eligibility Criteria:

- DoD beneficiary with HIV-1 infection
- $\geq$ 200 CD4 cells/mm^3
- Undetectable viral load, for at least the previous 8 weeks.
- Stable anti-retroviral regimen for $\geq$ 8 weeks
- Venous access sufficient for apheresis
- Karnofsky performance > 80%
- Informed consent

1.10 Exclusion Criteria:

- Inadequate organ function
- Lifetime history of CD4 count <200 cells/mm^3 on 2 consecutive measurements.
- Any previous history of gene therapy
- Recent IL-2 therapy or other treatment with investigational agent
- Pregnancy
- Some medications (hydroxyurea, corticosteroids and other immunosuppressants, chemotherapy, etc.)

1.11 Statistics:

Data analysis will be primarily descriptive in this pilot study. Variables describing safety of the treatment include the ACTG Adverse Events Grading Scale, Karnofsky scale and Seattle GVHD Grading System. Feasibility will be described by analysis of cell manufacturing data using medians with ranges or means with standard deviations.

The primary response variables for efficacy of treatment are the change in CD4 count, change in viral load, frequency of infected lymphocytes with replication competent HIV, and distribution of gene–marked lymphocytes in the blood and tissue. Data will be analyzed using repeated measures analysis of variance; data may be transformed to satisfy assumptions for normality.

The study will be analyzed on an intent to treat basis.

2 PROTOCOL OVERVIEW: SCHEMATIC OUTLINE